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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,050	10/27/2004	Gavril W Pastenark	62076(51590)	2704

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EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,050	PASTENARK, GAVRIL W	
	Examiner	Art Unit	
	Jody L. Karol	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/28/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the Response to Election/Restriction filed on 4/16/2008. Claims 1-25 are pending.

Election/Restrictions

1. Applicant's election **without** traverse of Group II claims 3-18 and 20-25 directed to methods of providing analgesia to a subject in need thereof comprising L-methadone and at least one opioid analgesic and the species election **without** traverse of morphine in the reply filed on 4/16/2008 is acknowledged.

Claims 1-2 and 10-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Accordingly, claims 3-9 and 20-25 are examined on the merits herein.

Priority

2. This application is a 371 of PCT/US03/09766 International Filing Date: 3/27/2003, which claims priority to Provisional Applications 60/367790 and 60/416414 filed 3/27/2002 and 10/7/2002 respectively. However, the name of the inventor in the signed declaration of the instant application (Gavril W. Pasternark) is spelled differently from the name of the inventor for the PCT Application and Provisional Applications (Gavril W. Pasternak). Thus, the inventors cannot be assumed to be the same inventor, and the instant application does not receive the benefit of the filing date of the PCT

Application, or the priority to the Provisional Applications to which the PCT Application claims benefit.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed on 2/28/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered.

Specification

4. The disclosure is objected to because of the following informalities: on page 15 of the instant specification, Table 1 is partially cut-off on the right side.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 3-5, 7-9 and 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Bolan et al. ("Synergy between μ Opioid Ligands: Evidence for Functional

Interactions among μ Opiod Receptor Subtypes," *J. Pharm. Exp. Ther.* 303:557-562, 2002).

Bolan et al. teaches a method of providing analgesia to mice by injecting 1 mg/kg of L-methadone and morphine (see page 559, Fig. 1 A). Bolan et al. further teaches that L-methadone significantly potentiated the analgesic activity of morphine (see page 559, column 2).

7. Claims 3-4, 7-9 and 2-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. ("Analgesics. I. Effect of Analgesic Combinations on Reaction Time in Rats," *Journal of Pharmacology and Experimental Therapeutics*, 1954, 108, pgs 336-339).

Smith et al. teaches a method of providing analgesia to rats, whose tails are exposed to a beam of light of constant intensity, by administering a combination of methadone and morphine via subcutaneous injection (see page 336, Materials and Methods, and pages 337). The methadone taught by Smith et al. is considered to be a racemic mixture of D and L racemates, and thus comprises L-methadone. Smith et al. further teaches administering methadone in a dosage of 1 mg/kg of body weight of the rat, and morphine in 4 mg/kg of body weight of the rat (see page 228, Table 2).

In regards to the recitation in claims 3 of "wherein the pharmaceutical composition is administered in an amount and duration sufficient to potentiate an antinociceptive response," the amounts and duration sufficient to obtain this effect is not defined in the specification. Therefore, claims 3-4 and 22-25 (all containing similar

recitations) are broadly interpreted as administering any amount of L-methadone and morphine in any manner or duration.

In regards to claims 24-25, the ability of compositions comprising L-methadone and morphine to potentiate an antinociceptive response is inherently present. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bolan et al. ("Synergy between μ Opioid Ligands: Evidence for Functional Interactions among μ Opioid Receptor Subtypes," *J. Pharm. Exp. Ther.* 303:557-562, 2002).

Bolan et al. is described *supra* as applied to claims 3-5, 7-9 and 20-25.

Bolan et al. does not explicitly teach administering L-methadone in a dosage range of 2 to 10 mg (per kg). However, Bolan et al. does teach that the ED_{50} of L-methadone is 1.9 ± 0.2 mg/kg.

It would have been obvious to one of ordinary skill in the art to optimize the dosage of L-methadone in the method of providing analgesia taught by Bolan et al. One of ordinary skill in the art would have been motivated to do so to provide the desired analgesic effects as the optimization of the result-effective parameters is obvious as being within the purview of skilled artisan.

10. Claims 5-6 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. ("Analgesics. I. Effect of Analgesic Combinations on Reaction Time in

Rats," *Journal of Pharmacology and Experimental Therapeutics*, 1954, 108, pgs 336-339) as applied to claims 3-4, 7-9 and 2-25 in view of Inturrisi (US 6,008,258).

The instant claims 5-6 are directed to methods of providing analgesia comprising administering a pharmaceutical composition comprising L-methadone and morphine, wherein the dosage range for L-methadone is from about 1 mg to about 60 mg, and 2 mg to about 10 mg. The instant claims 20-21 are directed to methods of providing analgesia comprising administering a pharmaceutical composition comprising L-methadone and morphine wherein the pharmaceutical compositions comprise a racemic mixture of DL methadone having at least 65% L-methadone.

Smith et al. is described *supra* as applied to claims 3-4, 7-9 and 2-25.

Smith et al. does not teach methods of providing analgesia wherein the methadone is a racemic mixture having at least 65% L-methadone. Furthermore, while Smith et al. teaches a dosage of 1 mg of methadone, Smith et al. does not explicitly teach the dosage ranges as claimed for L-methadone.

Interussi teaches that the L-isomer of methadone is responsible for the opioid properties, whereas the D-isomer is weak or inactive as an opioid (see column 3, lines 21-23). In an exemplary test, Interussi further teaches that L-methadone produces dose-dependent antinociception (analgesia) in rats with an ED_{50} value of 15.6 μg/rat, while D-methadone produced no antinociceptive effects at doses from 20 to 460 μg/rat. (see column 3, lines 51-57).

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ an increased amount of the active L-isomer of methadone as taught

by Interussi, in the racemic mixture of methadone used in the method of providing analgesia taught by Smith et al.

One of ordinary skill in the art would have been motivated to do so because the L-isomer of methadone is the active isomer of methadone in terms of providing opioid analgesia. Additionally, it would have been obvious to one of ordinary skill in the art to optimize the dosage of L-methadone. While the prior art references do not explicitly teach the dosage range of L-methadone, the determination of an optimal dosage of L-methadone by routine experimentation is obvious absence a showing of criticality of the dosage. One have ordinary skill in the art would have been motivated to optimize the dosage of L-methadone in order to achieve the desired analgesic effects.

The Applicants claim that the L-methadone and morphine are administered in an amount and duration sufficient to potentiate an antinociceptive response. The "potentiated antinociceptive response" is defined on page 10, lines 10-13 of the instant specification, as a pain-reducing response elicited through the synergistic effect of at least two opioids, in which the combined effect is greater than the sum of the effect produced by either opioid agent alone. It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably

commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). However, it is noted that the data presented to demonstrate the synergistic effect of L-methadone and morphine is not commensurate with the scope of the claims. For example, while the instant claims encompass all administration routes for L-methadone and morphine, the data presented in Example 1 on page 15 of the instant specification only demonstrates the interaction of L-methadone with opioids via subcutaneous injection. Furthermore, it is unclear how the additive (predicted) effect of L-methadone and morphine is calculated. The individual ED_{50} values are 1.9 and 4.7 respectively. It is believed that the additive ED_{50} value should be 3.3 instead of 3.11. In addition, the examiner also notes that not all opioid analgesic would have synergistic effects with L-methadone. For example, oxycodone, meperidine, and fentanyl do not produce synergistic effect when they are concomitantly employed with L-methadone (See Fig. 1A). Lastly, the Table 1 on page 15 of the specification is cut-off, and it is unclear if there is any data missing. Therefore, no clear and convincing unexpected results are seen to be present herein.

Conclusion

No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JLK

/San-ming Hui/
Primary Examiner, Art Unit 1617